## REMARKS

Upon entry of the present amendment, claims 20-52, 54-59, 61-106, 108-114, and 116-221 will be pending. Claims 22-30, 32-72, 74-84, and 86-142 have been withdrawn by the Examiner. Claims 53, 60, 107, and 115 have been cancelled. Claims 20 and 143 have been amended. Support for amended claim 20 can be found in the specification as filed, e.g., at page 76, lines 9-11, and at page 282, lines 14-16. Claim 143 has been amended to depend from claim 20. New claims 217-221 have been added. Claims 217-220 find support in previously presented claim 20. Support for new claim 221 can be found in the specification as filed, e.g., at page 80, lines 12-23.

A Substitute Sequence Listing and a Statement Accompanying Substitute Sequence Listing are being submitted herewith. Sequence SEQ ID NO:3 has been amended and finds support in original Fig. 4. Previously-submitted SEQ ID NO:3 is presented herein as SEQ ID NO:42.

Applicants submit that no new matter has been added.

Election/Restriction

Applicants note with appreciation that the Examiner has agreed to examine both the N13B and the N13Z species in the elected Group.

It is noted that claims 143-216 have been amended to depend from the elected Group.

Claim Interpretation

According to the Examiner at page 3,

> SEQ ID NO:3 of the instant specification numbers the residues of human hCGβ differently than is commonly accepted in the art. Specifically, the numbering is off by one amino acid. Thus, the mutation referred to by applicants as "N13B" does not exist in SEQ ID NO:3; the N residue is found at position 14 of SEQ ID NO:3.

Applicants disagree that the amino acid numbering used in the specification is different than numbering commonly accepted in the art. That point is further discussed *infra*, in the discussion of the indefiniteness rejection. Regarding numbering of residues in the claims, Applicants submit herewith a substitute sequence listing, in which SEQ ID NO:3 corresponds to the amino

acid numbering in the claims. SEQ ID NO:3 is supported by original Fig. 4. The substitute sequence listing also includes SEQ ID NO:42, which corresponds to previously-submitted SEQ ID NO:3. It is noted that SEQ ID NO:3 submitted herewith starts with Serine, while SEQ ID NO:42 begins with Proline and lists Serine as a second residue. Withdrawal of all claim interpretation objections is respectfully requested.

Specification and Title

The Office objected to the specification because "[t]he disclosure should be carefully reviewed for typographical errors. For example, at page 5, line 10, "hCH" should read --hCG--" (Office Action at page 3). The specification has been amended accordingly.

The Examiner also objected to the title as allegedly not descriptive. Without conceding to the substance of the objection, Applicants amended the title to: "Isolated Modified Human Chorionic Gonadotropin Proteins."

Withdrawal of all objections to the specification and the title is respectfully requested.

Rejections under 35 U.S.C. § 101

The Examiner rejected claims 20, 21, and 73 as allegedly being directed to non-statutory subject matter, stating that "the claims to not require that the claimed protein be isolated, purified, or otherwise show the hand of the inventor" (at page 3). Claim 20 has been amended to recite an isolated modified human chorionic gonadotropin (hCG). Claims 21 and 73 that depend from claim 20 are therefore similarly and properly directed to statutory subject matter. Withdrawal of all Section 101 rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 20, 21, 31, 73, and 85 have been rejected as allegedly being indefinite (at page 4). According to the Examiner:

> [t]he claims are indefinite because SEQ ID NO:3 of the instant specification numbers the residues of human hCGβ differently than is commonly accepted in the art. Specifically, the numbering is off by one amino acid. Thus, the mutation referred to by applicants as "N13B" does not exist in SEQ ID NO:3; the N residue is found at position 14 of SEQ ID NO:3. However, the art recognizes the intended mutation as being at position 13.

As discussed above, Applicants submit herewith a substitute sequence listing with a corrected SEQ ID NO:3. The substitute SEQ ID NO:3 corresponds to original Fig. 4, which begins with a Serine residue and lists the N residue at position 13. Thus, the numbering used in the claims, the specification, and SEQ ID NO:3 renders this rejection moot.

Further, the Examiner states that:

> [c]laim 20 is also indefinite because it is not exactly clear what hormone is being claimed. The preamble states that the claim is to "A human glycoprotein hormone family protein," which would indicate to the person of ordinary skill in the art a set of four hormones, LH, FSH, hCG and TSH. However, the body of the claim states that the claimed hormone must have an electrostatic charge altering mutation in the L1β hairpin loop structure of an hCGβ subunit. . . . Because of the use of a broad limitation (human glycoprotein hormone family protein) and a narrow limitation (hCGβ) in the same claim, the claim is indefinite.

Without conceding to the substance of the rejection, Applicants amended claim 20 to recite in the preamble "an isolated modified human chorionic gonadotropin (hCG) protein," obviating the rejection. For the sake of completeness, it is noted that the amendment was not necessary, as the wild type alpha subunit is identical among FSH, TSH, LH, and hCG proteins (see, e.g., specification at page 2, lines 6-7), and a skilled practitioner would understand that the claimed protein is hCG based on the language of the claims referring to the hCGβ subunit.

Finally, according to the Examiner:

> [c]laim 20 is further indefinite as the metes and bounds of the claim cannot be determined because there is no indication of the upper limitation of mutations that may occur, including whether or not said mutations are limited to the recited portions of the molecule, and whether or not any structure and/or function must be maintained.

Without conceding the issue, but solely to move claims toward allowance, Applicants amended claim 20 to further recite that said mutation results in said hCG protein exhibiting increased hCG bioactivity. As discussed in the specification at page 282, first full paragraph, at least two types of hCG-β subunit mutations (B75R and N77D) increased bioactivity of hCG. For example, both mutants showed increased progesterone production and cAMP level. The specification further outlines various methods of measuring hCG bioactivity (see, e.g., page 80, first full paragraph). Thus, the amended claim provides a clear outline of the types of mutations (at specific residues)

and the result of such mutations (the protein exhibiting increased hCG bioactivity). As such, it is a definite claim.

New claims 217-221 depend from claim 20 and are likewise definite. Claims 217-220 add specific types of mutations to the protein of claim 20. Claim 221 further defines the increased hCG bioactivity as increased progesterone production. Thus, the new claims define additional and specific characteristics of the proteins of claim 20.

Withdrawal of all indefiniteness rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 20, 21, 31, 73, and 85 as allegedly not being enabled by the specification (at page 5). Without conceding to the substance of the rejection, Applicants amended claim 20 and submit that the specification fully enables a skilled practitioner to *make* and *use* the claimed proteins. Examiner's arguments are addressed below, as they pertain to the amended claims.

Independent claim 20 is drawn, *inter alia*, to an isolated modified hCG protein comprising at least one electrostatic charge altering mutation at a specified region, wherein said mutation results in said hCG protein exhibiting increased hCG bioactivity. The specification provides ample teaching to enable a skilled practitioner *to make* such proteins. Amino acid mutation techniques are known in the art. Examples of evaluating mutants for their bioactivity are provided, e.g., at pages 79-81 of the specification as filed. In one cell-based assay, progesterone production is measured and "[t]he bioactivity of the mutant proteins tested is expressed as the percentage of wild type progesterone production displayed by the mutant proteins" (at page 81, lines 6-8).

The specification also allows skilled practitioners *to use* the claimed proteins. For example, at page 82, third and fourth full paragraphs, the specification discusses administration of the claimed proteins for treatment of disorders (e.g., hypogonadotropic hypogonadism), in which hCG is absent or decreased.

Thus, a skilled practitioner would be able to make and use the claimed protein based on the teachings of the specification.

According to the Examiner at page 5:

> The claims are extremely broad. There is no requirement for conservation of any activity. There is no requirement for possession of any activity. There is no upper limit on the number of mutations allowed, either in the specified region of the protein or elsewhere. All that is required is that there be *at least* one electrostatic charge altering mutation in the specified region. (emphasis in the original)

As discussed above, claim 20 has been amended to recite, *inter alia*, an isolated modified hCG protein comprising at least one electrostatic charge altering mutation, wherein said mutation results in said hCG protein exhibiting increased hCG bioactivity. Thus, the claimed proteins exhibit a specific activity, as well as comprise specific amino acid mutations, obviating the rejection. Applicants submit that a skilled practitioner would be able to introduce the specific mutations into hCG beta subunit and test the resulting mutants for bioactivity. As discussed above, the specification includes ample description of bioactivity assays (see, e.g., pages 79-81 of the specification as filed).

Moreover, the Examiner states at page 6:

> The relative skill in the art is high with respect to the ability to generate mutated proteins. However, the relative skill in the art is low with respect to being able to predict the effects of said mutations. One illustrative piece of art is Campbell et al., WO91/16922, cited by applicants, wherein specific residues from the beta subunits of each glycoprotein hormone were substituted into at least one of the other members of the family. However, those substitutions evince unpredictability, and do not even begin to address the scope of the pending claims.

As outlined above, amended claim 20 is drawn, *inter alia*, to proteins exhibiting increased hCG bioactivity. Testing for bioactivity, *i.e.*, for effects of the mutation, would not require undue experimentation given the teachings of the specification and state of the art. At pages 79-81, for example, the specification discusses immunoassays that can be used to analyze the ability of a mutant hCG to bind to or compete with wild-type hCG; cell-based assays that can be used to measure bioactivity; and immunoassays that can test half-life of the mutant protein. Such methods are well-known in the art and would not require undue experimentation to carry out and determine the bioactivity of generated mutants.

Further, unlike suggested by the Examiner, Campbell does not appear to focus on unpredictability of mutations. In fact, Campbell discusses the ability to study various functions of proteins due to the generation of the mutants, stating that:

> [t]he present invention utilizes DNA mutagenesis and gene expression to produce glycoprotein hormone analogs. These analogs have enabled identification of residues important for receptor binding and specificity, subunit interaction, and antibody binding (at page 5, lines 5-9; emphasis added).

Thus, Campbell does not support the nonenablement rejection of the present claims.

Finally, according to the Office:

> There is no specific guidance in the specification as to which species would have what properties. In fact, the specification at page 11 issues an invitation to experiment to determine what properties a molecule might have . . . . There are no working examples in the specification in which even a single mutein of hCG beta was made.

Applicants disagree. Amended claim 20 recites a protein comprising a specific mutation, wherein said mutation results in said hCG protein exhibiting increased hCG bioactivity. The specification provides support for this amendment, e.g., at page 76, lines 9-11, and at page 282, lines 14-16. Further, page 282 of the specification describes two experiments, in which two hCG beta subunit mutants were generated and analyzed. According to the specification, both the G75R and the N77D mutants (expressed as heterodimers with the wild type alpha subunit) induced higher levels of cAMP and progesterone production than did wild type hCG in a cell-based assay.

At least for the reasons presented above, independent claim 20 and its dependent claims are fully enabled by the specification. Withdrawal of all enablement rejections is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

The Examiner rejected claims 20, 73, and 85 as allegedly being anticipated by Campbell, stating that "Campbell et al. teach muteins of glycoprotein hormones. A species having the substitution N13E (an acidic residue) is disclosed as species C1; see table III at page 62" (Office Action at page 7). Without conceding to the substance of the rejection, but solely in the interest

of moving the claims toward allowance, Applicants amended claim 20 as discussed above and submit that it is not anticipated by Campbell.

Amended claim 20 is drawn to proteins comprising at least one electrostatic charge altering mutation, wherein said mutation results in said protein exhibiting increased hCG bioactivity. The mutations disclosed in Campbell Table III are hCG/TSH chimaeras designed to have multi-protein activities and not necessarily increased bioactivity. In fact, some of Campbell's hCG mutants show lower hCG activity. For example, hCG alpha-beta dimer F8 with a deletion mutation was shown to bind to LH receptors nearly as well (implying decreased binding) as hCG (see discussion of Figure 13 at page 50, lines 22-25). In particular, Campbell does not teach that its C1 species of hCG and TSH chimaera has increased hCG bioactivity. In fact, Campbell does not seem to discuss any bioactivity of the C1 species.

Therefore, because Campbell does not teach that its C1 species exhibits increased hCG bioactivity, it does not anticipate amended claim 20 or its dependent claims.

Withdrawal of all anticipation rejections is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 20, 21, 31, 73, and 85 have been rejected as allegedly being obvious over Moyle, U.S. Pat. 7,001,597 ("Moyle") (at page 8 of the Office Action). According to the Examiner,

> Moyle teaches muteins of hCG, which is produced in the form of a single chain gonadotropin. See Table 1, at column 44, which discloses numerous species within the mutation "N13X" in the hCG beta subunit. At column 45, lines 4-6, "N13X" is defined as "refers to the substitution of glutamine *or other amino acid* (emphasis added) for the hCG β subunit residue asparagine 13 and analogs." Moyle teaches that such analogs are useful for various fertility-associated uses, see column 41, which discusses the expected properties of particular analogs.

Without conceding the issue, Applicants amended claim 20 as discussed *supra*. Claim 20 and its dependent claims are not rendered obvious by Moyle. Claim 20 is drawn to proteins with at least one electrostatic altering mutation, wherein said mutation results in the protein exhibiting increased hCG bioactivity. Presently claimed proteins are not obvious in view of Moyle, whose disclosed proteins are significantly different from the presently claimed compositions.

First, it would not have been obvious to a skilled practitioner to substitute the N13 residue of hCG beta with a basic or an acidic residue based on Moyle, who, according to the Office's quote above, discusses indiscriminate types of substitutions. Amended claim 20 does not teach all possible types of N13 mutations, but instead specifies that they should be basic or acidic amino acid substitutions. Generally, out of the twenty amino acids, three are considered basic and two acidic. Moyle does not offer the motivation to modify it to arrive at the claimed proteins with these few possible mutations, disclosing all possible types of substitutions at N13. Thus, Moyle teaches a genus of mutants but does not disclose the claimed species.

Second, it would not have been obvious to obtain hCG beta mutants with increased bioactivity in view of Moyle. Wild type hCG is secreted during pregnancy to help maintain pregnancy (see, e.g., present specification at page 82, lines 8-9). Moyle teaches that the 2a analog of hCG beta (with N13X and N30X mutations) will have anti-LH activity and either facilitate ovulation or terminate pregnancy (Table 1 at col. 43 and Table 2 at col. 46). The actions of analog 2a will depend on the time at which it is administered (col. 41, lines 47-52). Thus, Moyle discusses use of hCG beta mutants with actions antagonistic to those of wild type hCG and thus with decreased bioactivity. Instead, the present claims are drawn to proteins with increased hCG bioactivity. The present specification further states that disorders (e.g., hypogonadotropic hypogonadism) where hCG is absent or decreased can be treated by administering the proteins of the present invention. Therefore, upon reading Moyle, a skilled practitioner would not be motivated to arrive at proteins with increased hCG bioactivity. In fact, Moyle suggests that hCG beta mutants with decreased bioactivity offer many advantages, i.e., inhibition of fertility via termination of pregnancy.

In summary, Applicants submit that presently claimed proteins as a whole would not have been obvious in view of Moyle. Moyle does not teach the specific claimed amino acid mutations that would result in the proteins' increased hCG bioactivity and offers no motivation or reasonable expectation of success to arrive at such proteins. The Examiner has not shown otherwise and therefore has not established a *prima facie* case of obviousness.

At least for the reasons presented above, claim 20 and its dependent claims are not rendered obvious by Moyle. Withdrawal of all obviousness rejections is respectfully requested.

## CONCLUSION

It is respectfully submitted that the above-identified application is now in a condition for allowance and favourable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

The Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 (with the exception of the issue fee) which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: February 14, 2008

Respectfully submitted,
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